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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,421	10/18/2001	Robert Sackstein	36459-501	1314

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
05/21/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/042,421	SACKSTEIN, ROBERT	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-25,28-32 and 62-65* is/are pending in the application.

4a) Of the above claim(s) *8-25 and 28-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 7 and 62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 01/31/2008, has been entered.

Claims 1 and 65 have been amended.

Claims 5-6, 26-27 and 33-61 have been canceled.

Claims 1-4, 7-25, 28-32 and 62-65 are pending.

Claims 8-25 and 28-32 have been withdrawn as being drawn to non-elected inventions.

Claims 1-4, 7 and 62-65 are being acted upon as the elected invention. .

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's amendment, filed 01/31/2008.

The rejections of record can be found in the previous Office Action.

3. Priority:

As indicated previously,
Upon a review of USSN 60/240,987, the priority application USSN 60/240,987 does not support the broader claims of the instant application.
USSN 60/240,987 appears directed to the distinct glycoform of CD44 as an L-selectin ligand on human hemopoietic progenitor cells, namely HCLL-CD44, that is a 98 kD KG1a CD44 membrane protein and which may have 120 / 130 kD bands that reflect isoforms that were designated CD44R2 and CD44Ra, respectively (see entire document, including Results). This provisional application was directed to identifying an unknown/ unassigned adhesion molecule, which was shown to have a previously unrecognized function of a well-characterized adhesion molecule (e.g. see pages 4-5, overlapping paragraph of USSN 60/240,987).

The instant claims are broader in scope than the particular adhesion molecule HCLL-CD44 identified and characterized in the priority document.

Further, it does not appear that priority USSN 60/240,987 provides sufficient written description for the claims nucleotide sequence comprising exons 1-5, 16, 18, and 20 of a human CD44 gene, wherein the CD44 polypeptide is a human CD44H, human CD44R1 or human CD44R2", "CD44 polypeptide comprises HECA-452 reactive sialyated, fucosylated N-glycans", wherein said glycosylated CD44 polypeptide is a ligand for both an E-selectin and L-selectin", and "wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide", as currently recited and as more broadly recited than previously described in USSN 60/240,987.

Also, it is noted that it does not appear that the priority USSN 60/240,987 provides sufficient written description for the limitations of the dependent claims, again as currently recited and more broadly recited than previously described in USSN 60/240,987.

Again, if applicant desires priority back to USSN 60/240,987, filed 10/18/2000;
applicant has been invited to point out and provide documentary support for the priority of the instant claims.

Applicant has been reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

A claim as a whole has only one effective filing date.
See e.g. Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997).

Applicant has been reminded that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed.
See Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

Therefore, the effective filing date of the instant claims has been deemed to be the filing date of the provisional USSN 60/297,474, filed 06/11/2001.

Applicant's amendment, filed 01/31/2008, does not dispute the effective priority of the instant claims.

4. Claims 1-4, 7 and 62-65 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sackstein et al. (Blood 89: 2773 – 2781, 1997), as further evidenced by Dimitroff et al. (J. Biol. Chem. 276: 47623 – 47631, 2001) and Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004) essentially for the reasons of record.

Applicant arguments, filed 01/31/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues the following.

Applicant respectfully submits that the disclosure of Sackstein fails to teach all the claim elements of the present claim. Specifically, Sackstein fails to disclose a purified preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans. That is, evening assuming, arguendo, that the polypeptide of Sackstein is the same as the recited polypeptide, the polypeptide of Sackstein was not purified. Sackstein describes a polypeptide that was not MECA-79 reactive and therefore was not immunoprecipitated from KG1a lysates using a MECA-79 antibody. Sackstein therefore fails to disclose a preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans having the recited level of purity. Accordingly, Sackstein cannot anticipate the present claims because this reference, in the least, does not disclose a purified preparation of a glycosylated CD44 polypeptide wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide, as is recited in the claims. Furthermore, Sackstein does not teach a preparation comprising any polypeptide in the form of a sterile aqueous solution, sterile aqueous dispersions, or sterile powder. Nothing disclosed in the other references cited by the Examiner as extrinsic evidence of anticipation (Dimitroff and Sackstein 2) changes these facts, nor do these references present any evidence to the contrary. Accordingly, Sackstein can not anticipate the present claims. Applicant requests that this rejection be withdrawn.

As noted previously, the inventor / author Sackstein does identify the HCELL / KG1a CD44 protein of the instant invention (see entire document, including the Abstract) as well as the immunoprecipitation of said HCELL / KG1a CD44 protein (see Results, including Figure 2 on page 2775 and Discussion) in the prior art rejection of record, namely Sackstein et al. (Blood 89: 2773 – 2781, 1997)

Therefore, the prior art is not limited to the asserted CD44 polypeptide backbone of the prior art.

Clearly, the prior art rejection of record Sackstein et al. (Blood 89: 2773 – 2781, 1997) describes and discusses the importance of sulfation in KG1a ligand, whether or not that the functional membrane glycoprotein L-selectin ligand whose binding activity was sulfate-dependent or not.

Again, note that the Discussion, particularly page 2780, column 1 of the prior art Sackstein et al. reference teaches the following.

The contribution of the sulfate modifications may relate to electrostatic forces via the localization of negative ions within discrete molecular determinants. Such a role for charge in L-selectin ligands is supported by the finding that unsulfated, but anionic polysaccharides such as polymers of phosphated mannose can bind to L-selectin. Within the KGla ligand, it is possible that glycosidic and/or amino acid modifications such as phosphorylation or the molecular composition of the discrete sugars or amino acids comprising the binding domain create a relevant anionic milieu. Present efforts are directed at isolating and characterizing the structure of this molecule. Although the precise structural features that direct binding activity for this and other naturally expressed membrane L-selectin ligands remain to be determined, the data presented here demonstrate that determinants conferring high-affinity recognition of L-selectin may vary among different cell types that express such ligands.

Also, note that the last line of the Abstract on page 2773 of 1 of the prior art Sackstein et al. reference states:

Identification of this novel ligand on non-endothelial cell type suggests that structural determinants conferring L-selectin binding may vary in a cell- and tissue-specific manner.

Again, it is the inventor Sackstein who teaches the hemopoietic cell L-selectin ligand which exhibits sulfate-independent binding activity that appears to be the same KG1a CD44 glycosylated polypeptide of the claimed invention (see entire document, including Abstract, Results and Discussion). Further, the Discussion describes the Results and the characterization of same KG1a CD44 isoform of the instant invention, including the nature of the sulfation-dependent epitope (see pages 2779-2780 of the Discussion)

Sackstein et al. teach the hemopoietic cell L-selectin ligand which exhibits sulfate-independent binding activity that appears to be the same KG1a CD44 glycosylated polypeptide of the claimed invention (see entire document, including Abstract, Results and Discussion).

Again it is maintained that given the teachings including the Discussion of efforts to isolating and characterizing the structure of the KG1a ligand by Sackstein et al. at the time the invention, one of ordinary skill would have immediately envisaged isolated HCELL / KG1a CD44 protein, including "isolated or purified protein that is substantially free of cellular materials or other contaminating protein from the cell or tissue source form which HCELL glycoprotein is derived or substantially freed form chemical precursors or other chemical when chemically synthesized , including being recombinantly produced, which is also free of culture medium (e.g. see page 11, paragraph 3 of the instant specification), thereby meeting the claimed limitation of "wherein the preparation comprises less that 5% of a polypeptide other than the glycosylated CD44 polypeptide".

In turn, one of ordinary skill in the art would have immediately envisaged isolated HCELL / KG1a CD44 protein in the form of "a sterile aqueous solution", as currently claimed; given the routine use of such "sterile aqueous solutions" to manipulate isolated proteins of use at the time the invention was made by the ordinary artisan.

The following of record is reiterated for applicant's convenience.

As pointed out previously and in further evidence, Dimitroff et al. discloses that the L-selectin ligand disclosed in Sackstein et al. (Blood 89: 2773 – 2781, 1997) reads on the instant hemopoietic cell E- and L-selectin ligand (see reference 18 cited in the Introduction, particularly page 47623, column 2, paragraph 1).

Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004) had been added as further evidence that the claimed HCLL is not novel or new.
"although initially considered to be a novel selectin ligand by the above biochemical criteria, mass spectrometry subsequently revealed that HCELL is not novel per se: it is a glycoform of a well-recognized integral membrane glycoprotein, CD44, that expresses the CLA epitope."
See page 1064, column 1, paragraph 1 of Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004).

Given the PTO's inability to manufacture products or to obtain and compare prior art products, the examiner properly shifted burden to applicant to establish, through objective evidence, that the very same KG1a CD44 polypeptide described by the inventor in by Sackstein et al. (Blood 89: 2773 – 2781, 1997), as well as by the inventor in the Dimitroff et al. (J. Biol. Chem. 276: 47623 – 47631, 2001). There is insufficient objective evidence that distinguishes the same or nearly the same KG1a CD44 isoforms in the prior art by the inventor from those CD44 isoforms currently encompassed by the instant claims.

Applicant's arguments have not been persuasive.

5. Claims 1-4, 7 and 62-65 are rejected under 35 U.S.C. § 102(b) as being anticipated by Stamenkovic et al. (EMBO Journal 10: 343 –348, 1991) (see entire document, including Figure 1) as evidenced by Sackstein (US 2003/0040607 A1) and Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004) essentially for the reasons of record.

Applicant arguments, filed 01/31/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues the following.

Stamenkovic does not teach the isolation and source of native CD44 immunoprecipitated from hematopoietic cells as the examiner suggests. As stated in the specification, there are a myriad of CD44 isoforms and glycoforms and the examiner presents no convincing evidence that the polypeptides of Stamenkovic are the same as those recited in the claims. At best, the rejection set forth on the Office Action is based on the principles of inherency in that the polypeptide of Stamenkovic is inherently the same as the recited polypeptide. Anticipation by inherency, however, requires that the prior art reference disclose each and every limitation of the claim. Nowhere in Stamenkovic is a disclosure of a preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans having the recited level of purity. In order for a prior art reference to anticipate a claim under the principles of inherency, the prior art reference must necessarily function in accordance with, or include, all claimed limitations in order to anticipate the claim. A conclusion that a result or characteristic may be present in the prior art reference is insufficient, as provided by M.P.E.P. § 2112.

Applicant respectfully submits that Stamenkovic fails to inherently disclose a polypeptide that is necessarily a glycosylated CD44 polypeptide comprising an amino acid sequence encoded by a nucleotide sequence comprising exons 1-5, 16, 17, 18, and 20 of a human CD44 gene, wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2, wherein the glycosylated CD44 polypeptide comprises sialylated, fucosylated glycans, wherein the glycosylated CD44 polypeptide is a ligand for E-selectin, L-selectin, or both, and wherein the preparation comprises less than 5% ofa polypeptide other than the glycosylated CD44 polypeptide. Indeed, Figure 3 of Stamenkovic demonstrates immunoprecipitation of the "hematopoietic form" of CD44 (CD44H) from CD44H transfected COS cells. The COS cell line is derived from kidney cells of the African Green monkey. As is explained in Sako et al. (Cell. 1993 Dec 17;75(6):1179-86; Attached hereto) COS cells are known to lack relevant fucosyltransferases essential for producing the sialofucosylated selectin binding determinants of the claimed glycosylated polypeptide. Specifically, explains as follows: COS cells do not bind P-selectin nor do they possess the appropriate glycosylation apparatus to synthesize Lewis" (Le") or SLe", presumed carbohydrate components of a P-selectin ligand (Larsen et al., 1990; Polley et al., 1991). Sako et al. at page 1179, right column, 4th line of the Results section; citations omitted. CD44H-transfected COS cells thus cannot produce the claimed glycosylated polypeptide as COS cells natively lack the relevant fucosysltransferase to create HCELL.

Moreover, none of the CD44 isoforms described in Stamenkovic have the same molecular weight profile as the species exhibiting L-selectin ligand activity. As is described in the specification at Example 4: Identification and Characterization of HCELL (page 17), the major L-selectin ligand activity can be found at 98 kD species. Stamenkovic does not disclose this species. Accordingly, the CD44 isoforms identified by Stamenkovic cannot be the same as those presently claimed.

Accordingly, Stamenkovic cannot anticipate the present claims because this reference, in the least, does not necessarily disclose a purified preparation of a glycosylated CD44 polypeptide wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide, as is recited in the claims. Furthermore, Stamenkovic does not teach a preparation comprising any polypeptide in the form of a sterile aqueous solution, sterile aqueous dispersions, or sterile powder.

Applicant is reminded that the claims are drawn to "a purified preparation of a glycosylated CD44 polypeptide, wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2".

Again, Stamenkovic et al. clearly teach the isolation of hemopoietic and epithelial forms of CD44 (see entire document), including that the hemopoietic form shows a species of molecular mass of approximately 80 kD (e.g., see page 344, column 2).

In consideration of the discrepancies often encountered in the art between protein molecular weight when determined by different methods, the hemopoietic form of CD44 taught by Stamekovic et al. appears to be the same hemopoietic form of CD44 described by the instant disclosure and encompassed by the claimed invention.

Again, as indicated previously, Stamenkovic et al. clearly teach the isolation and source of CD44, including immunoprecipitation of CD44 derived from hemopoietic cells (e.g., see The hematopoietic and epithelial CD44 isoforms show similar glysosaminoglcyan substitutions on page 345, column 2).

Also, as indicated previously; although applicant has argued that the reference teaches only expression by those cells such as COS or Namalwa that would not express HCELL.
The reference was not limited to expression by such cells.

Again, in contrast to applicant's focus on certain examples in the prior art reference and concerns about the glycosylation pattern of recombinantly expressed cells;
given the teachings including the teachings of isolating and characterizing as well as re-expression of each form of CD44 by Stamenkovic et al. at the time the invention,
one of ordinary skill would have immediately envisaged isolated hemopoietic CD44 isoforms from their original hemopoietic cell sources and not limited to the recombinant expression of said hemopoietic CD44 isoforms in COS cells only.

Again it is maintained that given the teachings including the teachings of isolating and characterizing as well as re-expression of each form of CD44 by Stamenkovic et al. at the time the invention,
one of ordinary skill would have immediately envisaged isolated HCELL / KG1a CD44 protein, including "isolated or purified protein that is substantially free of cellular materails or other contaminating protein from the cell or tissue source form which HCELL glycoprotein is derived or substantially freed form chemical precursors or other chemical when chemically synthesized , including being recombinantly produced, which is also free of culture medium (e.g. see page 11, paragraph 3 of the instant specification), thereby meeting the claimed limitation of "wherein the preparation comprises less that 5% of a polypeptide other than the glycosylated CD44 polypeptide".

In turn, one of ordinary skill in the art would have immediately envisaged isolated HCELL / KG1a CD44 protein in the form of "a sterile aqueous solution", as currently claimed;

given the routine use of such "sterile aqueous solutions" to manipulate isolated proteins of use at the time the invention was made by the ordinary artisan.

The following of record is reiterated for applicant's convenience.

Stamenkovic et al. teach the expression of CD44 transcripts in primary tumors of mesenchymal and epithelial origin, in normal epithelium and in lymphocytes (see page 344, column 1, paragraph 1 and Figure 2 as well as pages 345-346).

Also, Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004) has been added as further evidence that the claimed HCLL is not novel or new.

"although initially considered to be a novel selectin ligand by the above biochemical criteria, mass spectrometry subsequently revealed that HCELL is not novel per se: it is a glycoform of a well-recognized integral membrane glycoprotein, CD44, that expresses the CLA epitope."

See page 1064, column 1, paragraph 1 of Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004).

Therefore, as pointed out previously and in contrast to applicant's assertions, Stamenkovic et al. teach hemopoietic and epithelial forms of CD44, including encoding nucleotide and amino acids of CD44, which appear to be the same or nearly the same as the instant hemopoietic cell L-selectin / E-selectin ligand (HCELL), also referenced to as KG1a CD44, which is a glycoform of CD44 and comprising SEQ ID NO: 1, as set forth in Sackstein (US 2003/0040607 A1; see entire document, including Summary of the Invention, Examples, Table 1 and Claims).

Given the teaching of the structural characterization (e.g. amino acid and encoding nucleic acids) of CD44 isoforms as well as hemopoietic source of said CD44 isoforms (e.g CD44H referenced in Stamenkovic et al.) which is consistent with the instant disclosure as well as applicant's publication Sackstein (US 2003/0040607 A1) as well as the breadth of the instant claims, the prior art appears to read on the claimed polypeptides, in the absence of objective evidence to the contrary.

As indicated previously,

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

As set forth in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999):

"Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

The PTO's inability to manufacture products or to obtain and compare prior art products. Examiner properly shifted burden to applicant to establish, through objective evidence, that the very same KG1a CD44 polypeptides, including hemopoietic derived CD44 isoforms comprising SEQ ID NO: 1 described by Stamenkovic et al. and consistent with the teachings of the instant application and inventor's publication Sackstein (US 2003/0040607 A1), currently encompassed by the instant claims.

The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 145 USPQ 716, 718 (CCPA 1965). See MPEP 716.01(C).

Applicant's arguments have not been found persuasive.

6. Claims 1-4, 7 and 62-65 are rejected under 35 U.S.C. § 102(b) as being anticipated by Dougherty et al. (J. Exp. Med. 174: 1-5, 1991) (1449; #AJ) (see entire document) as further evidenced by Dimitroff et al. (J. Biol. Chem. 276: 47623 – 47631, 2001) and Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004) essentially for the reasons of record.

Applicant's arguments, filed 01/31/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues the following.

Dougherty fails to disclose forms of these polypeptides that comprise sialylated, fucosylated glycans. As stated in the specification, there are a myriad of CD44 isoforms and glycoforms and the examiner presents no convincing evidence that the polypeptides of the Dougherty are the same as those recited in the claims. At best, the rejection set forth on the Office Action is based on the principles of inherency in that the polypeptide of Dougherty is inherently the same as the recited polypeptide. Anticipation by inherency, however, requires that the prior art reference disclose each and every limitation of the claim. Nowhere in Dougherty is a disclosure of a preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans having the recited level of purity. In order for a prior art reference to anticipate a claim under the principles of inherency, the prior art reference must necessarily function in accordance with, or include, all claimed limitations in order to anticipate the claim.[4] A conclusion that a result or characteristic may be present in the prior art reference is insufficient, as provided by M.P.E.P. § 2112.

Applicant respectfully submits that Dougherty fails to inherently disclose a polypeptide that is necessarily a glycosylated CD44 polypeptide comprising an amino acid sequence encoded by a nucleotide sequence comprising exons 1-5, 16, 17, 18, and 20 of a human CD44 gene, wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2, wherein the glycosylated CD44 polypeptide comprises sialylated, fucosylated glycans, wherein the glycosylated CD44 polypeptide is a ligand for E-selectin, L-selectin, or both, and wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide. Indeed, as evidenced by the data of molecular weight, the CD44 molecules described in Dougherty are indeed different than those currently described in the specification. On page 2, 2nd column, 1st paragraph of the Results and Discussion section, Dougherty clearly indicates that the identified CD44 isoforms have a molecular weight of approximately 115 and 130 kD. As is described in the specification at Example 4: Identification and Characterization of HCELL (page 17), the major L-selectin ligand activity can be found at 98 kD species. Dougherty does not disclose this species. Accordingly, the CD44 isoforms identified by Dougherty cannot be the same as those presently claimed. Accordingly, Dougherty cannot anticipate the present claims because this reference, in the least, does not necessarily disclose a purified preparation of a glycosylated CD44 polypeptide wherein the preparation comprises less than 5% of a polypeptide other than the glycosylated CD44 polypeptide, as is recited in the claims. Furthermore, Dougherty

does not teach a preparation comprising any polypeptide in the form of a sterile aqueous solution, sterile aqueous dispersions, or sterile powder.

Applicant is reminded that the claims are drawn to "a purified preparation of a glycosylated CD44 polypeptide, wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2".

Again, Dougherty et al. clearly teach the isolation and molecular cloning of CD44R1 and CD44R2, as well as their expression on various hemopoietic cells and cell lines, including the KG1a cell lines.

Also, note in contrast to applicant's assertions,
Dougherty et al. does teach that the predominant CD44 species expressed by lymphocytes and other hemopoietic cell types has a molecular weight of approximately 85-95 kD and
that in additional species of approximately 115 kd and 130 kD are evident in the myelomonocytic cell line KG1a (see the first paragraph of Results and Discussion on page 2, column 2).

Given the teaching of the structural characterization (e.g. amino acid and encoding nucleic acids) of CD44R1 and CD44R2 isoforms as well as hemopoietic source of said CD44R1 and CD44R2 isoforms, which is consistent with the instant disclosure as well as instant claims 62-64 as well as the breadth of the instant claims, the prior art appears to read on the claimed polypeptides, in the absence of objective evidence to the contrary.

Again it is maintained that given the teachings including the Discussion of efforts to isolating and characterizing the structure of the KG1a ligand by Sackstein et al. at the time the invention,
one of ordinary skill would have immediately envisaged isolated HCELL / KG1a CD44 protein, including "isolated or purified protein that is substantially free of cellular materials or other contaminating protein from the cell or tissue source form which HCELL glycoprotein is derived or substantially freed form chemical precursors or other chemical when chemically synthesized , including being recombinantly produced, which is also free of culture medium (e.g. see page 11, paragraph 3 of the instant specification), thereby meeting the claimed limitation of "wherein the preparation comprises less that 5% of a polypeptide other than the glycosylated CD44 polypeptide".

In turn, one of ordinary skill in the art would have immediately envisaged isolated HCELL / KG1a CD44 protein in the form of "a sterile aqueous solution", as currently claimed;
given the routine use of such "sterile aqueous solutions" to manipulate isolated proteins of use at the time the invention was made by the ordinary artisan.

The following of record is reiterated for applicant's convenience.

With respect to the examiner's rebuttal with respect to the evidentiary references by Dimitroff et al. (J. Biol. Chem. 276: 47623 – 47631, 2001) and Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004),
See Section 5 above for the applicability of these references as well as the rebuttal in response to applicant's arguments.

Also, Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004) has been added as further evidence that the claimed HCLL is not novel or new.

"although initially considered to be a novel selectin ligand by the above biochemical criteria, mass spectrometry subsequently revealed that HCELL is not novel per se: it is a glycoform of a well-recognized integral membrane glycoprotein, CD44, that expresses the CLA epitope."

See page 1064, column 1, paragraph 1 of Sackstein (J. Invest. Dermatol. 122: 1061-1069, 2004).

Therefore, as pointed out previously and in contrast to applicant's assertions, Stamenkovic et al. teach hemopoietic and epithelial forms of CD44, including encoding nucleotide and amino acids of CD44, which appear to be the same or nearly the same as the instant hemopoietic cell L-selectin / E-selectin ligand (HCELL), also referenced to as KG1a CD44, which is a glycoform of CD44 and comprising SEQ ID NO: 1, as set forth in Sackstein (US 2003/0040607 A1; see entire document, including Summary of the Invention, Examples, Table 1 and Claims).

Products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

As set forth in Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999):
"Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

Where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, it has the authority to require the applicant to prove that the subject matter shown in the prior art does not possess the characteristics relied on. In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

Given the PTO's inability to manufacture products or to obtain and compare prior art products, the burden has been shifted to applicant to establish, through objective evidence, that claimed CD44 polypeptides are distinguishable from the very same or nearly the same KG1a CD44 polypeptides, including hemopoietic derived CD44H, CD44R1 and CD44R2 isoforms described by the prior art are607 A1), currently encompassed by the instant claims.

Applicant's arguments have not been found persuasive.

7. Claims 1-4, 7 and 62-65 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Sackstein et al. (Blood 89: 2773 – 2781, 1997) (of record)
AND / OR Stamenkovic et al. (EMBO Journal 10: 343 –348, 1991) (of record)
AND / OR Dougherty et al. (J. Exp. Med. 174: 1-5, 1991) (1449; #AJ)
in view of art known and practiced procedures to isolate and express isolated or purified proteins of interest at the time the invention was made,
as taught by Ni et al. (U.S. Patent No. 5,942,417) (892; of record),
as as taught by McEver et al. (U.S. Patent No. 6,124,267)
and as acknowledged on pages 19-24 of the instant specification and as evidenced by the following statements in the instant specification that it would be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired for the reasons of record.

Applicant arguments, filed 01/31/2008, have been fully considered but have not been found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues the following.

Sackstein discloses a glycoprotein L-selectin ligand express in KG1a cells that possess functional properties that overlap with the CD44 glycoprotein now claimed. Sackstein, however, fails to disclose a purified preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans. Evening assuming, arguendo, that the polypeptide of Sackstein is the same as the recited polypeptide, the polypeptide of Sackstein was not purified. Sackstein describes a polypeptide that was not MECA-79 reactive and therefore was not immunoprecipitated from KG1a lysates. Sackstein therefore fails to disclose a preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans having the recited level of purity.

Stamenkovic and Dougherty also fail to disclose the purified preparation of a glycosylated CD44 polypeptide comprising, inter alia, sialylated, fucosylated N-glycans. The examiner relies on the principles of inherency to apply these references to the instant claims. As is explained above, these references fail to disclose a purified preparation of a CD44 isoform necessarily having all of the elements of the claims.

The Examiner cites Ni and McEver to support the argument that one of ordinary skill in the art would have utilized the protein purification techniques disclosed in these references to isolate the ligand identified in Sackstein. For example, the examiner relied on Ni for its teaching of methods of isolating and expressing isolated proteins of interest, wherein "isolated encompasses remov[al] from its native environment, purified and produced by recombinant means." See Office Action at page 12. Sackstein, however, fails to sufficiently and specifically identify the ligand described therein to a degree that would permit a person of ordinary skill in the art to remove the ligand from its native environment, purify, and produce the ligand by recombinant means. For example, Sackstein fails to provide the amino acid sequence of the ligand that would permit the recombinant expression of the ligand. Accordingly, the combination of Sackstein and Ni would fail to produce the preparation of the claims.

The Examiner cites McEver for its disclosure that "the known manipulation and expression of interest that are associated with sialyated and fucosylated glycan and that interact with selectins." See Office Action at page 13, fist paragraph. The examiner specifically cites the columns 9-11 and 15-44, which provide guidance for the isolation and purification of recombinant proteins. As discussed above, however, Sackstein, fails to sufficiently and specifically identify the ligand described therein to a degree that would permit a person of ordinary skill in the art to recombinantly express the ligand. For example, Sackstein fails to provide the amino acid sequence of the ligand that

would permit the recombinant expression of the ligand. Accordingly, the combination of Sackstein and McEver would fail to produce the preparation of the claims.

To establish prima facie obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art. M.P.E.P. § 2143.03. The primary references of Sackstein Stamenkovic, and/or Dougherty fail to disclose or suggest at least one of the elements recited in the claims, as mentioned above. The Office Action does not rely on the secondary references to cure the deficiencies of the primary references, which forces the conclusion that the combination of the prior art references would not teach every element of the claims and therefore fails to render obvious the present claims. As such, applicant respectfully submits that the rejection fails to establish a prima facie case of obviousness.

Applicant is reminded that the claims are drawn to "a purified preparation of a glycosylated CD44 polypeptide, wherein the CD44 polypeptide is CD44H, CD44R1, or CD44R2".

Again, the prior art references clearly teach the isolation of the claimed hemopoietic CD44H as well as CD44R1 and CD44R2, including their expression on various hemopoietic cells and cell lines, including the KG1a cell lines.

Applicant's arguments and the examiner's rebuttal with respect to the teachings of Sackstein et al. (Blood 89: 2773 – 2781, 1997), Stamenkovic et al. (EMBO Journal 10: 343 –348, 1991) and Dougherty et al. (J. Exp. Med. 174: 1-5, 1991) (1449; #AJ) have been addressed above.

Applicant's arguments appear to ignore the clear teachings in the prior art, including the inventor's own prior art reference Sackstein et al. (Blood 89: 2773 – 2781, 1997), that the hemopoietic CD44H as well as CD44R1 and CD44R2 were known in the prior art.

For example, note the following from page 1064, column 1 of Sackstein et al. (J. Invest. Dermatol. 122: 1061-1069, 2004) (892; of record)

As stated above, the bone marrow microvasculature is like that of skin in that it displays constitutive expression of E- and P-selectin (Schweitzer et al, 1996; Frenette et al, 1998). There is increasing evidence these molecules play important roles in trafficking of primitive hematopoietic cells into bone marrow (Frenette et al, 1998; Mazo et al, 1998; Hidalgo et al, 2002; Katayama et al, 2003). Although the identity of the true HSC is debated, for the purposes of this review we will consider CD34+ cells lacking lineage-specific markers (i.e., CD34+/lineage- cells) as the representative population of HSC. Human HSC express PSGL-1 and another selectin ligand, HCELL (Oxley and Sackstein, 1994; **Sackstein et al, 1997**; Dimitroff et al, 2000, 2001a; Sackstein and Dimitroff, 2000). HCELL was initially identified operationally as an L-selectin ligand, and was distinguished from all other L-selectin ligands by a number of biochemical features: (1) Sulfation-independent binding activity; (2) functional resistance to O-sialoglycoprotease digestion; (3) absence of MECA79 antigens; and (4) L-selectin binding determinants that were expressed on N-glycans rather than O-glycans (Oxley and Sackstein, 1994; Sackstein et al, 1997; Sackstein and Dimitroff, 2000). **Although initially considered to be a "novel" selectin ligand by the above biochemical criteria, mass spectrometry subsequently revealed that HCELL is not novel per se: it is a glycoform of a well-recognized integral membrane glycoprotein, CD44, that expresses the CLA epitope (i.e., is recognized by mAb HECA452). In contrast to PSGL-1 that displays CLA on O-glycans, however, the CLA determinant(s) and the E-/L-selectin binding sites of HCELL are on N-glycans.**

Again it is maintained that given the teachings of isolating and characterizing the structure of the claimed hemopoietic CD44H as well as CD44R1 and CD44R2, including their expression on various hemopoietic cells and cell lines, including the KG1a cell lines.

one of ordinary skill would have immediately envisaged or readily have expected the isolation of HCELL / KG1a CD44 / CD44H / CD44R1 / CD44R2 glycosylated proteins including "isolated or purified protein that is substantially free of cellular materials or other contaminating protein from the cell or tissue source form which HCELL glycoprotein is derived or substantially freed form chemical precursors or other chemical when chemically synthesized , including being recombinantly produced, which is also free of culture medium (e.g. see page 11, paragraph 3 of the instant specification), thereby meeting the claimed limitation of "wherein the preparation comprises less that 5% of a polypeptide other than the glycosylated CD44 polypeptide" at the time the invention

In turn, one of ordinary skill in the art would have immediately envisaged or readily employed isolated HCELL / KG1a CD44 protein in the form of "a sterile aqueous solution", as currently claimed;

given the routine use of such "sterile aqueous solutions" to manipulate isolated proteins of use at the time the invention was made by the ordinary artisan.

It has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See In re Rosicky, 125 USPQ 341 (CCPA 1960).

Also, given the use of adhesion molecule- / selectin-related proteins of interest for various diagnostic/therapeutic utilities as taught by McEver et al. (e.g., see columns 11-15) and by Ni et al. (e.g., see columns 28-37),

it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide CD44 polypeptides of interest

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See In re Rosselet, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." Motorola, Inc. v. Interdigital Tech. Corp., 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See KSR Int'l Co. v. Teleflex Inc., 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to isolate, characterize and employ CD44 proteins of interest at the time the invention was made,

incorporating of HCELL / KG1a CD44 / CD44H / CD44R1 / CD44R2 glycosylated proteins into purified preparations, including forms of sterile aqueous solutions, dispersions and powders would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing purified preparations of glycosylated CD44 polypeptides of interest.

The following of record is reiterated for applicant's convenience.

Again, it is noted that Dougherty et al. (J. Exp. Med. 174: 1-5, 1991) (1449; #AJ) as well as McEver et al. (U.S. Patent No. 6,124,267) as well as applicant's acknowledgement in the instant specification that it would be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired.

The teachings of Sackstein et al. and Stamenkovic et al. are set forth above and are of record in the rejection under 35 U.S.C. § 103(a) of record.

As indicated above

Dougherty et al. teach the isolation and molecular cloning of CD44R1 and CD44R2, as well as their expression on various hemopoietic cells and cell lines, including the KG1a cell lines.

Given the teaching of the structural characterization (e.g. amino acid and encoding nucleic acids) of CD44R1 and CD44R2 isoforms as well as hemopoietic source of said CD44R1 and CD44R2 isoforms, which is consistent with the instant disclosure as well as instant claims 62-64 as well as the breadth of the instant claims, the prior art appears to read on the claimed polypeptides, in the absence of objective evidence to the contrary.

Dougherty et al. differs from the claimed invention by not being explicit in terms of certain structural or functional characteristics as currently claimed.

Sackstein et al., Stamenkovic et al. and Dougherty et al. differ fom the claimed invention by not disclosing the purity of their referenced CD44 glycoforms or that they do not exemplify the isolation of their referenced CD44 glycoforms via known and practiced recombinant methods to isolate and express proteins of interest by the ordinary artisan at the time the invention was made.

Ni et al. teach the known and practiced methods of isolating and expressing isolated proteins of interest, including its application to CD44 proteins at the time the invention was made (see entire document, including Summary of the Invention, Detailed Description and Examples). Also, note that Ni et al. teach that isolated encompasses removed from its native environment, purified and produced by recombinant means (e.g. see column 18, paragraph 1).

McEver et al. teach the known manipulation and expression of proteins of interest that are associated with sialylated and fucosylated glycans and that interact with selectins, including the use of fucosyltransferases in the expression and anyalysis of said proteins of interest at the time the invention was made (see entire document, including Detailed Description of the Invention, including Expression Systems on columns 9-11 and Examples on columns 15-44).

Consistent with the prior art of record and newly added McEver et al.,

Pages 19-24 of the instant specification acknowledges the art known and practiced procedures to isolate and express isolated or purified proteins of interest at the time the invention was made.

For example, page 20, paragraph 2 of the instant specification states that

It would be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired.

In this Section on HCELL Recombinant Expression Vectors and Host Cells,

It is noted that applicant also relies upon prokaryotic and eukaryotic cells, including CHO or COS cells, as well as tissue-specific regulatory elements known and practiced at the time the invention was made.

Given the teachings of Sackstein et al., Stamenkovic et al. and Dougherty concerning the expression and role of the claimed CD44 glycoforms, one of ordinary skill in the art would have isolated and produced CD44 glycoforms via various known means at the time the invention was made, including recombinant means as a standard practice to investigate the role and use of said CD44 glycoforms in physiological events. Given the standard practices of isolating and recombinantly expressing antigens, including adhesion molecules such as CD44 glycoforms as well as the known manipulation and expression of proteins of interest that are associated with sialylated and fucosylated glycans and that interact with selectins, including the use of fucosyltransferases in the expression and anyalysis of said proteins of interest at the time the invention was made, one of ordinary skill in the art had a reasonable expectation of success in preparing the claimed CD44 glycoform in preparation comprising less than 5% of the CD44 glycoform other than the glycosylated CD44 polypeptide. The advantages of isolated and purified molecules of interest, including adhesion molecules as CD44 glycoforms, were well known and practiced in the art at the time the invention was made in order to study and characterize the molecule / protein of interest for structure-function relationships as well as to employ such proteins for a wide variety of utilities associated with the molecule / protein of interest. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

8. Claims 1-4, 7 and 62-65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of copending USSN 11/032,256 for the reasons of record.

The instant and copending claims appear to be drawn to the same or nearly the same CD44 glycosylated isoforms, including HCELL. Therefore, the copending claims and the instant claims appear to anticipate or render obvious one another.

Applicant's amendment, filed 01/31/2008, does not address the double patenting rejection of record.

9. The previous rejection under the judicially created doctrine of obviousness-type double patenting with respect to the claims of USSN 11/272,453 has been withdrawn in view of the amended claims in USSN 11/272,453.

10. It is noted that applicant has a number of copending applications drawn to CD44 glycosyalted isoforms, particularly to those associated with HCELL.

Applicant is invited to clarify which applications should be subject to rejections under the judicially created doctrine of obviousness-type double patenting.

11. No claim allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on (571) 272-0878.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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